Substituted dihydroisoquinolinones by iodide-promoted cyclocarbonylation of aromatic α-amino acids

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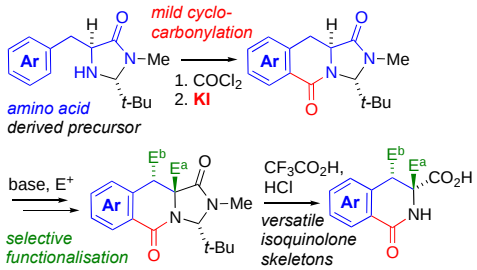
Supporting Information Placeholder



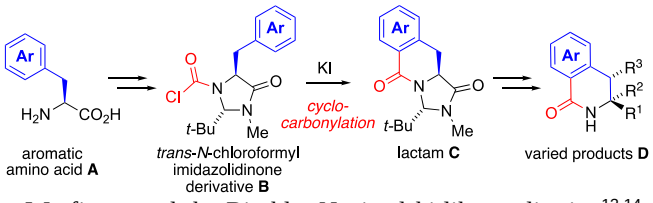
ABSTRACT: Imidazolidinone derivatives of a range of aromatic α-amino acids, on treatment with phosgene and potassium iodide, undergo a mild Bischler-Napieralski-style cyclocarbonylation reaction that generates a tricyclic lactam by insertion of a C=O group between amino acid nitrogen and the *ortho* position of the aryl substituent. Regio- and diastereoselective functionalization of the lactam generates a library of substituted dihydroisoquinolinones and their congeners in enantioenriched form.

The dihydroisoquinoline ring system is found in some key biologically active compounds,[1] not least among them the Amaryllidaceae alkaloids such as narciclasine and pancratistatin.[2,3] Dihydroisoquinolines have also been identified as key scaffolds for fragment-based drug discovery.[4] Among synthetic approaches to this ring system, reactions in which an aromatic amine precursor is cyclised with addition of one or two carbon atoms are the most common approaches.[5] For example, aromatic amides or hydroxamic acids give dihydroisoquinolones by metal catalysed C-H activation with alkenes or alkynes[6] or palladium catalysed cyclocarbonylation of amines.[7,8] Alternatively, Bischler-Napieralski-style cyclisation can give dihydroisoquinolinones by activation of *N*-carbamoyl derivatives of secondary homobenzylic amines using highly electrophilic reagents such as triflic anhydride,[9,10] or Lewis-acid promoted cyclisation of carbamoyl chlorides.[11,12]

In this paper we report a practical and operationally simple carbonylative cyclisation that converts aromatic amino acids into substituted dihydroisoquinolinones and their analogues in an efficient, versatile and stereoselective manner, without the need for powerful activating agents or Lewis acids. The reaction involves the activation of an easily formed, stable carbamoyl chloride derivative using iodide, and gives rise to architecturally varied motifs that can readily be derivatised stereoselectively to yield families of enantiomerically-enriched cyclic amino acid derivatives.

The cyclofunctionalisation at the core of the method is outlined in Scheme 1. The method entails the formation of the *N*-chloroformyl derivative **B** of a *trans* imidazolidinone, followed by its cyclisation by intramolecular Friedel-Crafts acylation to yield the lactam **C**. This lactam may be readily elaborated by further alkylation and ring-cleavage reactions to provide a diverse range of products very efficiently from simple amino acid precursors **A**.

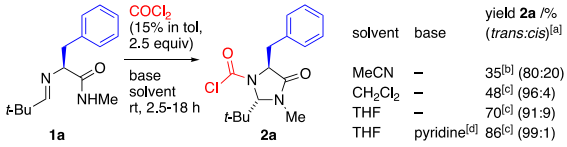
Scheme 1. Cyclocarbonylation of aromatic amino acids.



We first noted the Bischler-Napieralski-like cyclisation[13,14] of **B** to **C** as a side reaction that occurs when using the unusually unreactive carbamoyl chloride **B** as an electrophile. Given the limitations of classical Bischler-Napieralski conditions when applied to amino acids,[13,14] this reaction appeared to offer a very appealing way to make cyclic amino acid derivatives under mild conditions. Preliminary studies indicated that a cyclisation product was formed only from the *trans* diastereoisomer of **B**, so we first set out to optimise a practical method for the *trans*-selective synthesis of *N*-chloroformylimidazolidinones **B**.

N-Chloroformylimidazolinones may be formed non-diastereoselectively by treatment of pivaldimine derivatives of amino acids with triphosgene in the presence of base.[15] In order to develop a method for the diastereoselective synthesis of *trans* imidazolidinones, the cyclisation of Phe-derived pivaldimine **1a** was investigated (Scheme 2). Simply stirring the imine **1a** with phosgene at room temperature gave good selectivity for the *trans* diastereoisomer, but generally with low yields, probably as a result of precipitation of an intermediate hydrochloride salt. Improved yields were obtained in THF, and addition of pyridine 30 min after the start of the reaction returned the chromatographically stable *trans N*-chloroformylimidazolidinone **2a** in excellent yield (Scheme 2). Triphosgene also gave good *trans* diastereoselectivity but lower yields than phosgene.

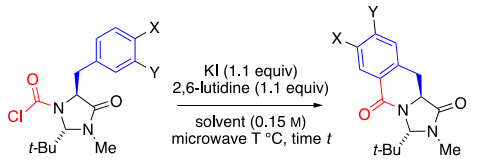
Scheme 2. Diastereoselective formation of *trans N*-chloroformyl imidazolidinones.



[a]Diastereoisomeric ratio by NMR of crude reaction mixture; [b]Yield of mixture determined by NMR using internal standard; [c]Isolated yield of major diastereoisomer; [d]Added 30 min after start of reaction.

Using these optimal reaction conditions, a broad series of *N*-chloroformylimidazolidinones **2a-m** (see Supporting Information) were made from their corresponding amino acid pivaldimine precursors **1** with excellent *trans* diastereoselectivity. The *trans* carbamoyl chlorides were remarkably stable, and each of **2a-2m** could be purified by chromatography on silica without difficulty. They were also rather unreactive as electrophiles, and their reaction with neutral nucleophiles necessitated the use of KI[16] to increase their electrophilicity. During the KI-promoted reaction of **2a** with an aniline,[15] we identified a cyclic by-product, which became the sole product when **2a** was heated with potassium iodide alone. This product, the benzo-fused lactam **3a** (Table 1) is evidently formed by an intramolecular Friedel-Crafts acylation that amounts to a Bischler-Napieralski cyclisation of **2** to **3**. The reaction was optimised with **2a** and its electronically varied derivatives **2b-d**, as shown in Table 1.

Table 1. Optimisation of the cyclocarbonylation



entry	SM	time	solvent	t /°C	product, yield /%
1	**2a**	2 h	tol	170	**3a**, 90
2	**2b**	2 h	tol	170	**3b**, 97
3	**2b**	10 s	CH_3CN	150	**3b**, 100 (91:9)[a]
4	**2c**	2 h	tol	170	**3c**, 48 (71:29)[b,c]
5	**2c**	1 h	CH_3CN	170	**3c**, 96 (76:24)[c]
6	**2c**	30 min	CH_3CN	120	**3c**, 94 (95:5)[c]
7	**2c**	5 min	CH_3CN	150	**3c**, 92 (98:2)[c]
8	**2d**	4 h	tol	200	no reaction[d]
9	**2d**	30 min	CH_3CN	170	**3d**, 6[d]
10	**2d**	30 min	DMF	120	**3d**, 30[d]

[a]Isolated with minor 2,3-dimethoxy substituted regioisomer **3b'**. Ratio determined by ^{1}H NMR; [b]SM recovered in 49% yield; [c]Isolated with a minor 2-fluoro substituted regioisomer **3c'**. Ratio determined by ^{1}H NMR. [d]Using 2.0 equiv lutidine.

Treatment of *trans* phenylalanine-derived carbamoyl chloride **2a** under activating conditions of KI (1.1 equiv) and 2,6-lutidine (2.0 equiv) in dry toluene under microwave irradiation at 170 °C for 2 h provided the cyclised product **3a** in 90% yield (entry 1). The more electron-rich DOPA derivative **2b** gave a yield of 97% of **3b** under these conditions (entry 2), but also turned out to be highly reactive in acetonitrile, cyclising quantitatively within 10 seconds of reaching 150 °C (entry 3). Under these conditions, a small amount of the 2,3-disubstituted regioisomer **3b'** was also formed by attack on the ring *ortho*, rather than *para*, to the 3-MeO substituent.

When the 3-fluorophenylalanine derivative **2c** was heated with the same reagents in toluene, the reaction did not go to completion even after 2 h (entry 4). This reaction produced 34% of the regioisomer **3c** formed by cyclisation *para* to the 3-F substituent, alongside 14% of the *ortho* regioisomer **3c'** and 49% recovered starting material. Changing the solvent to acetonitrile accelerated the reaction, but still gave poor regioselectivity (entry 5). Improved selectivity was ensured by lowering the temperature: at 120 °C the two regioisomers were formed in 89% and in 5% yield after 30 min (entry 6). Shortening the reaction time also appeared to improve regioselectivity, suggesting equilibration between the regioisomers: at 150 °C, only 2% of the minor regioisomer was formed, and the major product was isolated in 90% yield (entry 7).

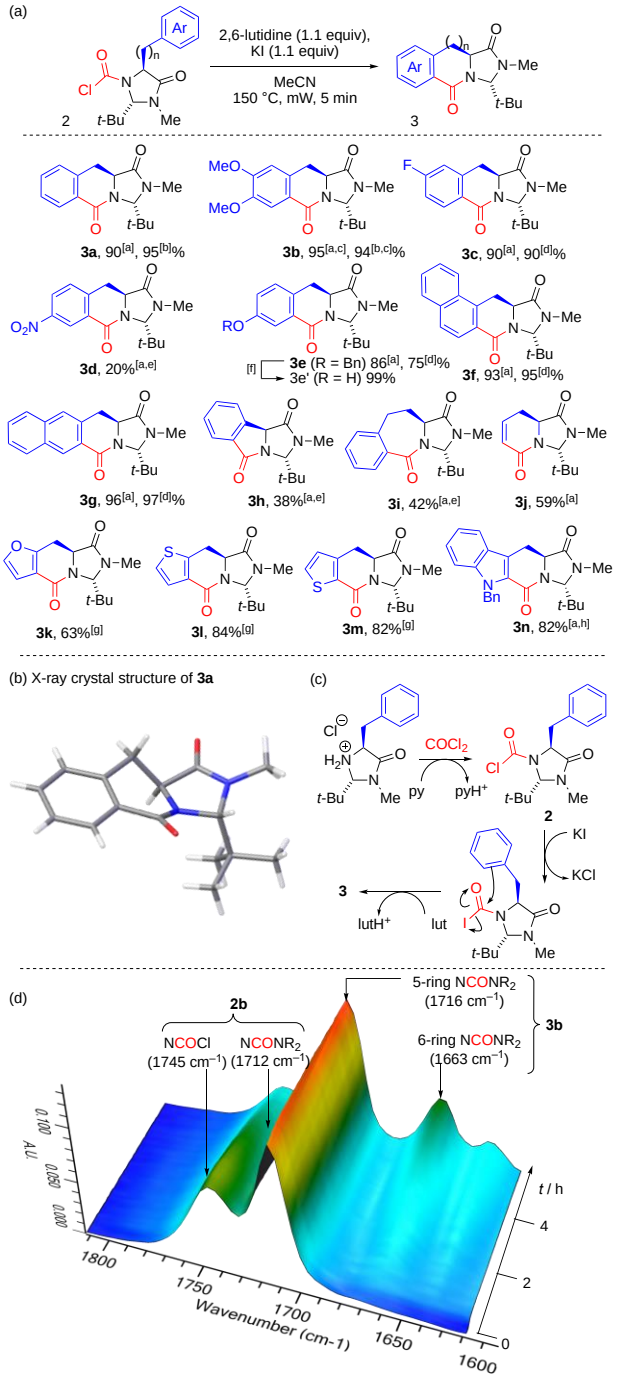
Cyclisation of the 4-nitrophenylalanine derivative **2d** was unsuccessful in toluene (starting material recovered) or acetonitrile (6% product and many by-products) even after prolonged reaction time and elevated temperature (entries 8, 9). Changing the solvent to DMF did however allow a 30% yield of the product **3i** to be isolated from other by-products (entry 10). As is usual for Friedel-Crafts substitutions, the reaction is evidently heavily dependent on the electronic effects of the substituents on the aryl ring, and is accelerated by a polar solvent. Nonetheless, it is remarkable that the acylation is successful with a fluoro or nitro-substituted ring using a carbamoyl chloride electrophile in the absence of a Lewis acid.

The optimal conditions identified for the cyclisation of **2** were applied to a range of aromatic, heteroaromatic and unsaturated amino acid derivatives shown in Scheme 3. Cyclisations on up to 10 g scale were successful not only with the phenylalanine derivatives **2a-2d**, but also with the tyrosine derivative **2e**, and with 1- and 2-naphthylalanine derivatives **2f** and **2g**, each of which cyclised in >90% yield. The retained relative stereochemistry of product **3b**, and therefore presumably other products as well, was confirmed by X-ray crystal structure[17] (Scheme 3b). Other ring sizes (5-membered

in **3h**; 7-membered in **3i**) formed after more extended reaction times, albeit in lower yield. An aliphatic Friedel-Crafts cyclisation of the allylglycine derivative **2j** gave dihydropyridone **3j**, and the nucleophilic furan and thiophene heterocycles of **2k-m** gave **3k-m** by attack at either the 2- or 3-position. The indole-containing product **3n** was also formed, but without isolation of the *N*-chloroformylimidazolidinone **2n**: the reactivity of the indole precursor **1n** is such that attempted formation of **2n** by the method of Scheme 3 led directly to the cyclised product **3n**, even without heating or KI.

We presume that KI promotes formation of a transient carbamoyl iodide[18] and thence maybe a carbamoyl cation,[19] with lutidine neutralising the acid formed during the acylation (Scheme 3b). The reaction of **2b** to give **3b** was followed by in situ infra-red spectroscopy (Scheme 3d). Over a period of 4 hours at 70 °C, direct conversion of **2b** to **3b** was noted, with no detectable intermediate. Any carbamoyl iodide intermediate must react faster than it forms.[20]

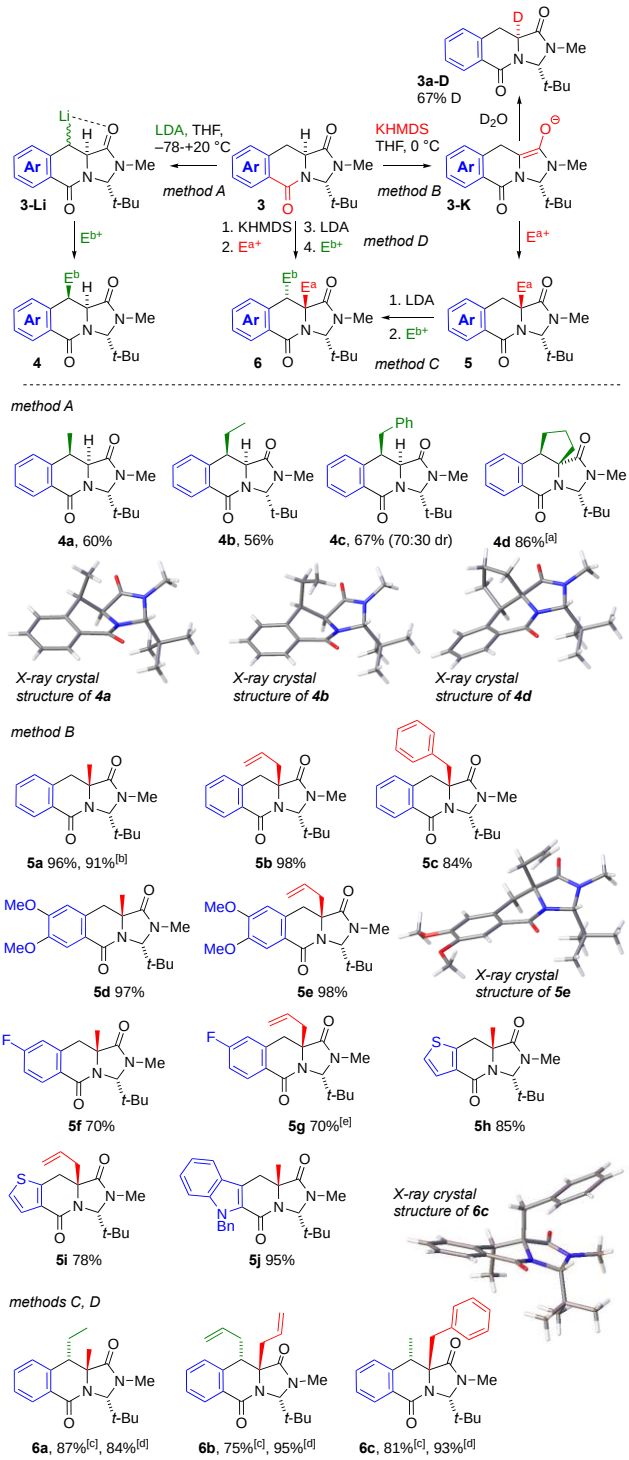
Scheme 3. (a) Cyclisation of a range of N-chloroformylimidazolidinones; (b) X-ray crystal structure of **3a**; (c) Proposed mechanism for the cyclisation; (d) in-situ infra-red trace for the cyclisation of **2b**



[a] < 1 g scale at 0.15 M; [b] 10 g scale at 1 M; [c]for 10 s; [d] 2-5 g scale at 0.5-1 M; [e]with 2.0 equiv lutidine, for 3 h; [f]H_2, Pd/C, EtOH, 18 h; [g]On 1 g scale at 0.15 M; [h]Formed directly from **1n**.

Imidazolidinones are valuable intermediates in the synthesis of quaternary amino acids by alkylation of their enolate derivatives.[21] The enantiopure products of the cyclisation contain an imidazolidine motif amenable to diastereoselective alkylation, directed by the *tert*-butyl substituent. **3a** was thus alkylated by treatment with base followed by an electrophile (Scheme 4).

Scheme 4. Regioselective alkylations of **3**.



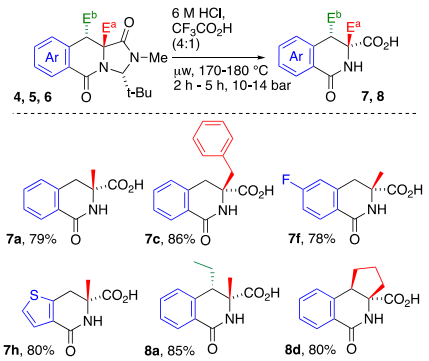
Method A: 1. Degas in THF; 2. E^+ (10 equiv) then LDA (2 equiv) –78 °C-rt; Method B: 1. KHMDS (1.5 equiv), THF, 0 °C, 15 min, 2. E^+ (5 equiv), 0 °C-rt, 2 h; Method C: 1. LDA (2 equiv), –78 °C, THF; 2. E^+ (5 equiv) –78 °C-rt, 2 h; Method D: 1. KHMDS (1.5 equiv), THF, –78 °C, 15 min, 2. E^+ (1 equiv), –78 °C-rt, 2 h; 3. LDA (3 equiv), –78 °C, THF; 4. E^+ (10 equiv) –78 °C-rt, 2 h; [a]Using 4 equiv LDA; [b]Using LiHMDS; [c]Using method C; [d]Using Method D; [e]Using 2 equiv KHMDS. Relative configurations of **5a** and **6a** were assigned by NOE.

Alkylation of the indigo-violet solution generated by deprotonation with LDA occurred at the benzylic position β to the imidazolidinone carbonyl group, to give **4a** (from MeI) and **4b** (from EtI) with full diastereoselectivity.[22] X-ray crystallography[17] (Scheme 4) and NOE experiments confirmed the relative stereochemistry of the products **4a** and **4b**, which are consistent with both retentive quench of the coordinated anion **3-Li** and with alkylation *anti* to the *tert*-butyl group. Quenching with benzyl bromide similarly gave the β-alkylated product **4c**, but as a 70:30 mixture of diastereoisomers.[23] Formation of an extended 'arylogous' enolate **3-Li** at the β position is possible, but it seems unlikely that the β proton is thermodynamically more acidic than the α; plausibly, benzylic β-lithiation is directed by coordination to the amide carbonyl group,[24] and is favoured over removal of the encumbered proton at the ring junction *cis* to the *tert*-butyl group.[25]

Enolate formation was evident in the synthesis of the valuable spirocycle **4d**, which was formed in 86% by treating **3a** first with 1,3-dibromopropane and then with two portions each of 2 equiv of LDA at –78 °C (X-ray crystal structure:[17] Scheme 4). We expected a weaker base, or one with a less coordinating counterion, to be more selective for enolisation of the amide. **3a** was therefore treated instead with KHMDS at 0 °C for 30 min, and the anion, this time red, quenched with D_2O (Scheme 4). **3a-D** was returned with 67% incorporation of D at the α-position (by NMR analysis of the crude mixture). By treating the substrate with KHMDS (1.5 eq) at 0 °C for 3 h in THF (0.1 M) followed by methyl iodide (5 eq), the α-methylated product **5a** was formed as a single diastereoisomer in 96% yield (Scheme 4). A similar result (91%) was obtained with LiHMDS. Excellent yields of single diastereoisomers of **5b** and **5c** were likewise obtained with allyl bromide and benzyl bromide. Alkylation of **3e, b, l, n** likewise gave excellent yields of diastereoisomerically pure products **5d-5j**. The stereochemistry of **5e** was confirmed by X-ray crystallography (Scheme 4).

A second alkylation of the products **5** was possible by treatment with LDA at –78 °C for 30 min, followed by a second electrophile. The products **6a-c** were formed as single diastereoisomers for which NOE studies (of **6a**) and X-ray crystallography[17] (of **6c**) conformed that the new alkyl group lies *anti* to both the first-introduced alkyl group and the *tert*-butyl group. Double alkylation can be achieved in a one-pot reaction by first forming an enolate with KHMDS and secondly with LDA. By this method (method D) yields of **6a-c** were higher than the stepwise alkylation procedure.

Scheme 5. Hydrolysis of imidazolidinones



The products **4-6** contain an imidazolidinone motif which is prone to acid-catalysed hydrolysis. As shown in Scheme 5 valuable carboxyisoquinolone products **7** and **8** are formed by microwave irradiation in a mixture of hydrochloric and trifluoroacetic acid.[26]

In summary, mild carbonylative cyclisation of aromatic amino acids may be achieved by intramolecular Friedel-Crafts acylation of *trans N*-chloroformylimidazolidinones, promoted simply by potassium iodide. The product lactams may be further functionalized by regio- and diastereoselective alkylation, and the imidazolidinones may be hydrolysed to reveal enantiopure heterocyclic carboxylic acids of potential value in drug discovery programmes.[4]

Supporting Information

Full experimental details and NMR spectra of all new compounds.

Acknowledgements

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